HCV Treatment Duration in HIV/HCV Genotype 1 Co-infected Patients. Results of a Multicenter Randomized Trial

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61st AASLD – Abstract 83

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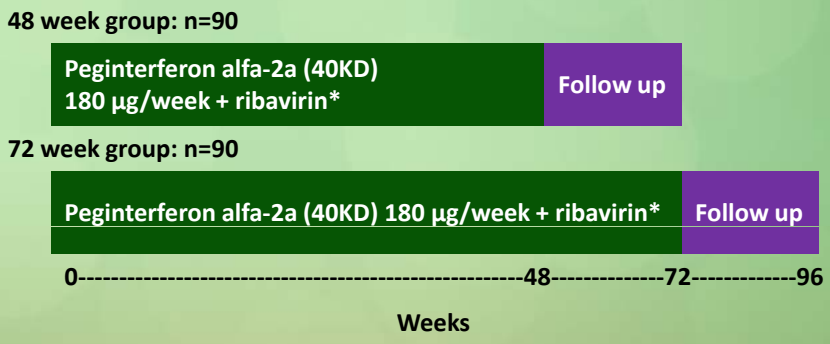
How Long to Treat in HIV/HCV GT 1 Coinfected Patients ?

- Background:
  - Peg-IFN plus ribavirin therapy for 48 weeks is currently recommended for HIV/HCV coinfected patients in the AASLD practice guidelines [1]
  - In the EACS hepatitis guidelines 72 weeks of treatment with Peg-IFN plus ribavirin are recommended for GT1 patients not achieving RVR but do have at least a 2log drop in HCV-RNA at week 12[2]

1 Ghany MG al. AASLD Practice Guidelines Hepatology 2009;49:1335-74
2 Rockstroh J et al. HIV Medicine 2008;9:82-88

Study Design

- A phase IV open label, randomized (1:1), multicenter (17 centers in Brazil), parallel group study



*Ribavirin dose 1000 mg/day (<75 kg body weight) or 1200 mg/day (≥75 kg body weight)

Patient Disposition

	48 week group	72 week group
Safety Population	82	86
ITT Population	80	85
Per protocol population	77	79

- Safety population: all patients that received at least one dose of the study medication, including protocol violators
- ITT population: all genotype 1 patients that received at least one dose of the study medication
- Per protocol population: all patients who completed the study excluding protocol violators

Baseline Characteristics (ITT)

	48 week group (n=80)	72 week group (n=85)
Mean age	42	42
Male, n (%)	49 (61)	69(69)
Race, n (%)		
Caucasian/White	28(35)	35(41)
Other	52(65)	50(59)
Mean weight, kg	68	69
Mean HCV RNA, log_{10} IU/mL	6.6	6.6
HCV RNA ≥800,000 IU/mL, n (%)	60(77)	61(73)
Cirrhotic (F3/F4), n (%)	11(14)	16(20)
ALT quotient, n (%)		
>1-2	39(51)	38(48)
>2-5	19(25)	22(28)
>5	1(1)	2(3)
HIV RNA undetectable, n (%)	64(79)	60(70)
CD4 >350 cells/mm^3, n (%)	61(78)	57(70)
HAART baseline, n(%)	69(86)	63(74)

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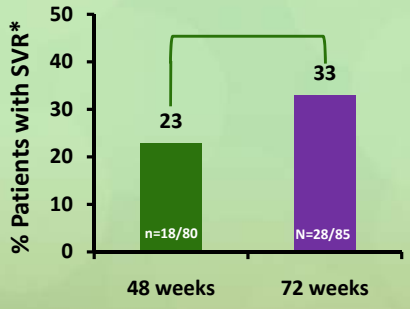
Virologic Response Rates (HCV RNA <50 IU/mL) 24 Weeks Post End-of-Treatment (SVR)

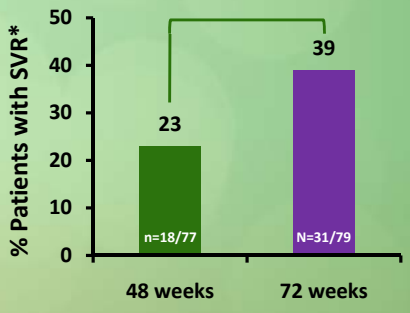
ITT Population

Treatment difference 10%
(95% CI -0.01-26.6): p=0.0536



Per Protocol Population

Treatment difference 16%
(95% CI -0.00-28.9): p=0.0374



* SVR = sustained virologic response, defined as undetectable (<50 IU/mL) HCV RNA as measured by the Roche COBAS AMPLICOR HCV Test at 24 weeks post-completion of the treatment period

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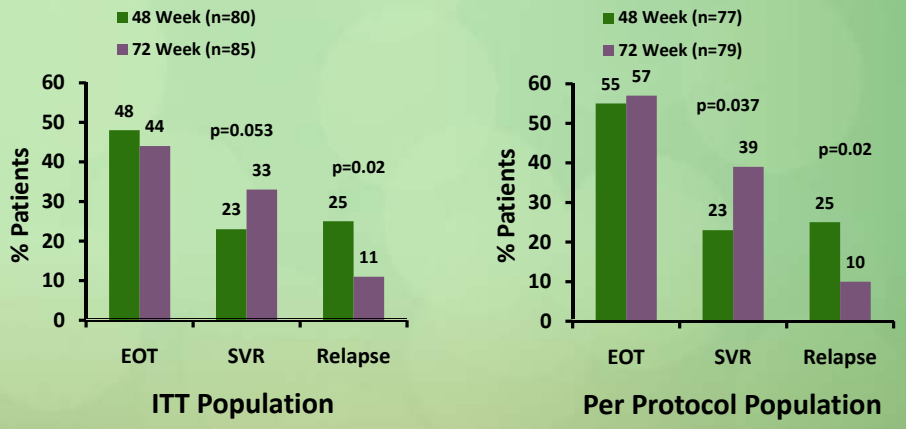
Treatment Outcomes



EOT = end of treatment.
SVR = sustained virologic response, defined as undetectable (<50 IU/mL) HCV RNA as measured by the Roche COBAS AMPLICOR HCV Test at 24 weeks post-completion of the treatment period

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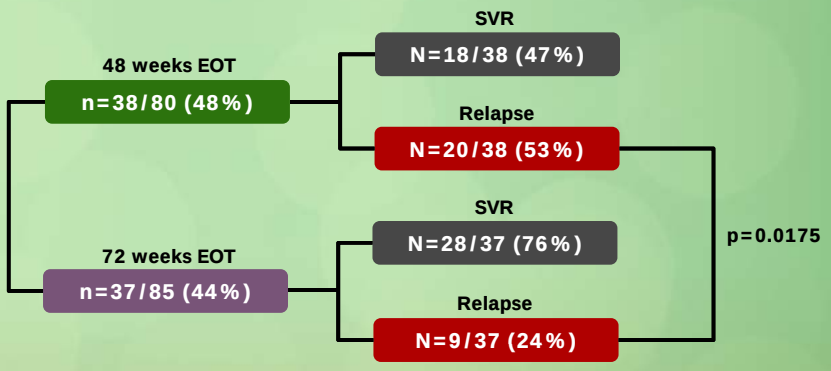
Outcomes in Patients with Undetectable HCV RNA at End of Treatment (ITT)



Relapse 24 weeks after end of therapy was significantly higher in the 48 week group versus the 72 week group

Similar results in the per protocol population, without SVR: 48 weeks 51%; 72 weeks 22%; p=0.0150

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Key Safety Data*

n (%)	48 week group (n=82)	72 week group (n=86)
All body systems		
Total patients with ≥1 AE	80 (98)	82 (95)
Total patients with ≥1 SAE	7 (9)	12 (14)
Total number of SAEs	11	15
Deaths	**0**	**0**
Dose reduction due to AE		
Peg-IFN dose reductions	10/76 (13)	12/82 (16)
Ribavirin dose reductions	21/76 (28)	15/82 (18)
Total withdrawals	15 (18)	27 (31)
Withdrawal due to AE	7 (9)	5 (6)

* Safety population

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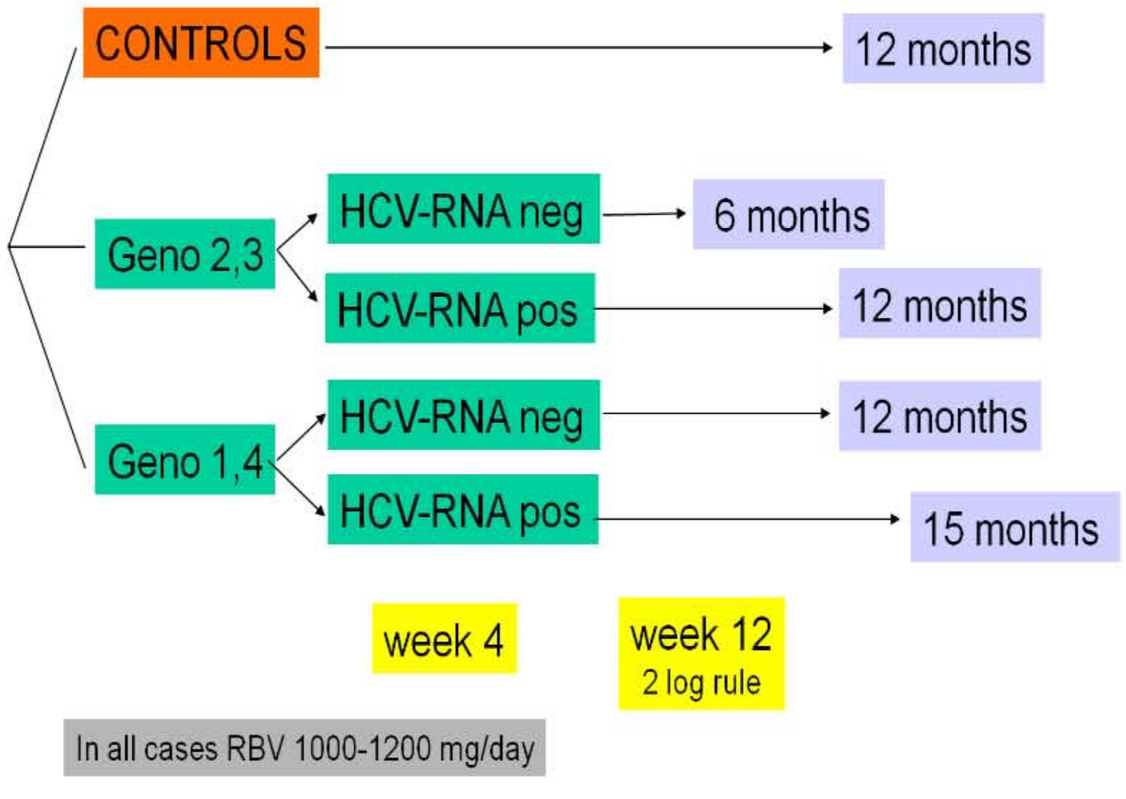
Length of Peginterferon-Ribavirin Therapy According to HCV Genotype and Rapid Virological Response in HIV/HCV Coinfected Patients: The EXTENT Trial

Pablo Barreiro, Paula Tuma, Antonio Rivero, Miguel Cervantes, Ignacio Santos, Ángela Camacho, Eugenia Vispo, Victor Asensi and Vincent Soriano, on behalf of the EXTENT Team

Background: Treatment of hepatitis C is less effective in HIV/HCV patients. Optimization of therapy is crucial, so that only patients with true chances for response should complete therapy for the appropriate duration. Given HCV G2/3 and RVR predict SVR in this population, length of therapy might be individualized accordingly.

Methods: Efficacy of pegIFN-alfa2b plus RBV was examined in HIV/HCV patients randomized to different lengths of treatment: 6 mo. G2/3 RVR+, 12 mo. G1/4 RVR+ or G2/3 RVR-, and 15 mo. G1/4 RVR-.



Results: A total of 185 HIV/HCV patients were enrolled (43 years-old, 75% males, 89% former IDUs, 85% under HAART, CD4 count 570 cells/μL, HCV-RNA 6.1 IU/mL, 73% >500,000 IU/mL, 67% G1/4. Liver fibrosis by METAVIR was 32% F0F1, 25% F2, 28% F3 and 15% F4.
RVR+ in 17 (16%) patients with G1/4 and in 27 (49%) with G2/3 ($p<0.001$). Overall 66 (36%) patients achieved SVR, 32 (26%) with G1/4 and 34 (55%) with G2/3 ($p<0.001$). Among HCV G1/4, SVR occurred in 11 (65%) patients RVR+ treated for 12 mo. and in 13 (62%) patients RVR- treated for 15 mo. ($p=0.9$); however, only 8 (9%) G1/4 patients RVR- treated for 12 mo. attained SVR ($p<0.01$). Among HCV G2/3 patients, SVR was seen in 12 (60%) patients with RVR treated for 6 mo. and in 17 (77%) patients without RVR treated for 12 mo. ($p=0.3$); and only 1 (17%) patient without RVR treated for 6 mo. attained SVR ($p=0.01$).

HCV genotype	RVR	Planned length of RX	SVR (%) by ITT
1 or 4	Yes	12 mo.	11/17 (65%)
	No	12 mo.	8/85 (9%)
	No	15 mo.	13/21 (62%)
2 or 3	Yes	6 mo.	12/20 (60%)
	No	6 mo.	1/6 (17%)
	No	12 mo.	17/22 (77%)

Conclusion: In HIV/HCV coinfected patients, extension of HCV therapy improves SVR rates in G1/4 without RVR. Shortening therapy to 6 months may be offered to G2/3 patients with RVR.

Increasing Frequency of Hepatocellular Carcinoma in HIV-Infected Patients.

A Pilot Study in 7 Countries in North & South America and Europe.

Jorge Daruich[1], Luciana Kikuchi[2], David E. Kaplan[3], Emma Page[4], Erica Palys[5], Nicolás Merchante[6], Manuel Márquez Molero[7], Rafiullah[8], David Rimland[9], Matthew Goetz[5], Mark Nelson[4], Juan A. Pineda[6], Kristen M. Marks[10], Norbert Bräu[8, 11], Liver Cancer in HIV Study Group*

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Background

- The incidence of HCC overall has been rising worldwide.
- Cases of HCC in HIV-positive patients have only recently been reported, and their frequency over time is unknown.

Methods

- **Retrospective analysis in 31 centers in 7 countries *(dark gray on map):***
  - North America: Canada and United States
  - South America: Argentina and Brazil
  - Europe: Germany, Spain and United Kingdom

Sites from countries in light gray are awaiting IRB/EC approval

- **All HCC cases in HIV-infected patients from 1995-2010 with data on initial presentation.**

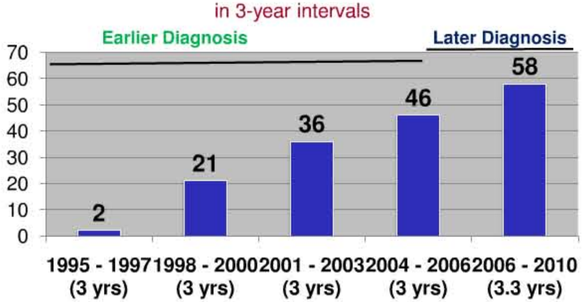
N=163

- Diagnosis by AASLD criteria (Bruix & Sherman, Hepatology, 2005)
- **Patients were divided into**

Earlier Diagnosis: 1995 – 2004 n=79
Later Diagnosis: 2005 – 2010 n=84

Increasing Frequency

in 3-year intervals



Patient Characteristics

	Diagnosis 1995-2004 n=79	Diagnosis 2005-2010 n=84	P
Age (yrs), Mean ± SD	52 (±8.8)	52.4 (±7.9)	0.65
Male Sex	77 (98%)	77 (92%)	0.105
Race/Ethnicity			
White	**32 (41%)**	**45 (54%)**	
Black	31 (39%)	33 (39%)	**0.083**
Latino	**13 (17%)**	**5 (6%)**	
Asian + other	3 (4%)	1 (1%)	
Etiology of HCC			
Chronic Hepatitis C	59 (75%)	61 (73.5%)	
Chronic Hepatitis B	18 (23%)	21 (25%)	0.78
Non-Viral (Alcohol, NASH)	2 (2.5%)	1 (1.2%)	
Excessive Alcohol Consumption	31 (43%)	27 (34%)	0.24
Child-Turcotte-Pugh Score, Mean ± SD	**7.0 (±1.89)**	**6.5 (± 1.60)**	**0.045**
Stage A	39(49%)	51(61%)	
Stage B	31(39%)	25(30%)	0.302
Stage C	9 (11%)	7 (8%)	
Prior HCC Screening	33 (44%)	49 (56%)	0.16
HIV RNA <400 copies/ml	**40 (51%)**	**58 (72%)**	**0.008**
Log10 HIV RNA, mean	**2.82**	**2.25**	**0.007**
CD4+ Cells, Mean (per mcl)	**277**	**357**	**0.009**

HCC Tumor Characteristics

	Diagnosis 1995-2004 n=79	Diagnosis 2005-2010 n=84	P
Hepatic Lesions			
Solitary Tumors	36(46%)	47(57%)	0.16
Multiple Tumors	43(54%)	36(43%)	
Diffusely Infiltrative Tumors			
Median Size Largest Lesion (cm), Range	4.0 (1.8-20)	4.5(0.5-18)	0.883
Portal Vein Thrombosis	12(79%)	19 (83%)	0.213
Extrahepatic Metastases	15(19%)	9 (11%)	0.145
AFP level			
Median (ng/ml)	**602**	**144**	**0.026**

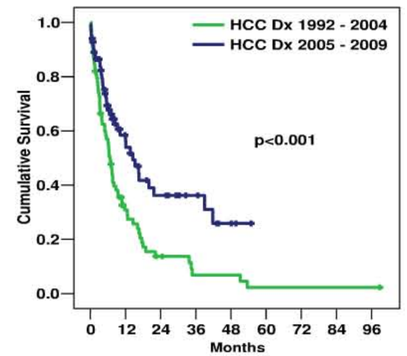
HCC Staging

	Diagnosis 1995-2004 n=79	Diagnosis 2005-2010 n=84	P
BCLC Stage, n (%)			
A	21 (27%)	27 (33%)	
B	17 (22%)	17 (21%)	0.57
C } Advanced	26 (31%)	26 (31%)	
D } Incurable	9 (11%)	13 (16%)	
CLIP Score, Mean ±SD	2.0	1.8	0.38

HCC Therapy

	Diagnosis 1995-2004 n=79	Diagnosis 2005-2010 n=84	P
Potentially Curative Therapy	25 (32%)	24 (29%)	
Radiofrequency Ablation (RFA)	13	9	
Ethanol Injections	8	2	
Surgical Resection	4	10	
Liver Transplantation	0	3	
Effective, Non-Curative Therapy	16 (20%)	28 (33%)	0.16
Transarterial Chemoembolization	16	17	
Sorafenib	0	11	
No Therapy	38 (48%)	32(38%)	

Survival



At Risk:

Diagnosis 1995 – 2004	79	18	7	3	3	1	1	1	1
Diagnosis 2005 – 2010	84	26	13	8	3				

Median survival
Diagnosis 1995 – 2004 6.8 months
Diagnosis 2005 – 2010 14.5 months

Summary and Conclusion

1) **The frequency of HCC in HIV-infected patients is rising in selected countries**
2) **Compared to patients with a diagnosis before 2005, patients diagnosed 2005 or later have**
   - **a) better control of HIV RNA levels,**
   - **b) higher CD4+ cells,**
   - **c) higher CTP scores and**
   - **d) lower AFP levels.**
   - **e) better survival**

To contribute your cases of HCC in HIV patients
for further studies, please contact:
Norbert Bräu
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ww.HCCinHIV.org

** This abstract is dedicated to Edmund J. Binihave , MD, MPH (1967 – 2010) who contributed greatly to this study, and who would have been a co-author*

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